

# CDC's Clinical Studies of Daily Oral Tenofovir for HIV Prevention



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June 2005

## Research Rationale

### Why is CDC launching tenofovir HIV prevention trials?

CDC is sponsoring these trials because safe and effective new approaches to HIV prevention are urgently needed. Worldwide, an estimated 14,000 people continue to become infected every day (over 5 million per year). In the United States alone, an estimated 40,000 people become infected each year. Although behavior change programs have contributed to dramatic reductions in the number of annual infections in the United States and many other nations, far too many people remain at high risk.

With an effective vaccine years away, there is mounting evidence that antiretroviral agents may be able to play an important role in reducing the risk for transmission. Researchers believe that an HIV drug approved by the Food and Drug Administration—tenofovir disoproxil fumarate (tenofovir, brand name Viread)—taken daily as an oral preventive, is one of the most important new prevention approaches being investigated today.

If proven safe and effective, this approach could help address the urgent need for a female-controlled prevention method for women worldwide who are unable, because of cultural and other barriers, to negotiate condom use. Furthermore, if effective, tenofovir, could provide an additional safety net for all men and women at risk due to sexual or drug-using behaviors, when combined with reducing the number of sexual partners, HIV counseling and testing, condom

use, use of sterile syringes, and other prevention measures.

### How would tenofovir work to protect against HIV infection?

The concept of providing a preventive before exposure to an infectious agent is not new. For example, travelers to an area where malaria is common are advised to take medication before and during travel to prevent the disease. The medicine to prevent illness is then already in their bloodstream if they are exposed to the malaria parasite.

Researchers believe that the same concept may work to protect people from HIV infection. Theoretically, if HIV replication can be inhibited from the moment the virus enters the body, it may not be able to establish a permanent infection.

### What data suggest that this approach may be safe and effective?

Several sources of data suggest that an antiretroviral drug, taken regularly, may prove effective in reducing a person's risk for infection:

- Providing a single dose of the antiretroviral drug nevirapine to HIV-infected women during labor and to their newborns immediately after birth has reduced the risk for mother-to-child transmission of HIV about 50%.
- In observational studies, the antiretroviral drug zidovudine, taken soon after exposure and continued for several weeks, has been associated with an 80% reduction in the risk of HIV infection among health care workers after

needlesticks or other accidental exposures.

- Finally, animal studies have shown that tenofovir, administered before and immediately after a single retroviral exposure, can prevent the transmission of a virus similar to HIV in monkeys.

The safety and efficacy of tenofovir for the treatment of HIV infection has been well established in clinical studies and medical settings. The U.S. Food and Drug Administration licensed the drug for use as an HIV treatment in adults in October 2001, and over 150,000 HIV-infected patients around the world have now used the drug. Among these patients, tenofovir has resulted in a relatively low level of side effects and little development of drug resistance, compared to other HIV treatments. The most common side effects include nausea, vomiting, and loss of appetite.

One of the key objectives of these trials is to determine for certain whether the drug is safe and well tolerated by HIV-negative persons; and safety will be closely monitored throughout the trials. Researchers expect side effects to be even less common in the healthy, HIV-negative volunteers in these HIV prevention trials.

## Trial Designs and Objectives

### What specific CDC studies are planned?

CDC is sponsoring three separate trials, which together are designed to answer important questions about the safety and efficacy of daily oral tenofovir for several of the populations now at greatest risk for infection worldwide: heterosexual men and women in Botswana, injection drug users (IDUs) in Thailand, and men who have sex with men (MSM) in the United States. In all, the trials will involve 3,200 participants. The trials are being conducted in collaboration with (a) the Botswana Ministry of Health, (b) the Bangkok Metropolitan Administration and the Thailand Ministry of Public Health, and (c) the San Francisco Department of Public Health and the AIDS Research Consortium of Atlanta.

### What are the goals of these trials?

The Botswana and Thailand trials are primarily designed to determine if once-daily oral tenofovir is safe and effective in reducing HIV transmission among young heterosexual men and women, and intravenous drug users, respectively. The U.S. trial is designed to evaluate the safety and tolerability of the once daily regimen among men who have sex with men, but will not be large enough to evaluate its effectiveness in reducing HIV transmission. Much larger, multi-city studies will be required to assess efficacy among this population, should safety be demonstrated.

All three studies are also designed to address several issues that will be critical to the design of future studies, as well as HIV prevention and treatment programs.

**Impact on behavior:** Understanding the potential impact of a daily drug regimen on HIV risk behaviors will be critical should tenofovir prove effective in reducing HIV transmission. One of the greatest risks, as efforts progress to identify new biomedical prevention approaches, is that persons at risk for HIV infection will reduce their use of proven behavioral prevention strategies. Because no single strategy will be 100% effective against HIV transmission, reducing transmission will require determining how to best integrate all available prevention strategies—both biomedical and behavioral. During the trials, all participants will receive state-of-the-art HIV risk-reduction counseling.

**Adherence and acceptability:** Even if these trials demonstrate that tenofovir can reduce HIV transmission, we must understand whether persons at risk will be willing and able to maintain the daily regimen. These trials will therefore closely examine participants' adherence to, and acceptance of, a daily oral regimen of tenofovir.

**Resistance:** A key question about resistance will be addressed during the trials. Although resistance to tenofovir is uncommon among HIV-infected persons when used in combination with other

drugs, it is unclear how often resistance may develop if prophylaxis fails and persons become infected with HIV while taking tenofovir alone. The result could be HIV-infected persons for whom tenofovir could not be used for treatment.

Regular testing with a rapid HIV test, combined with immediate discontinuation of study pills if participants become infected, should help guard against the development of drug resistance during the trial. Additionally, resistance testing will be provided to all persons infected during the trial and will be continued for 12 months after infection is detected. These data will provide important information on the degree to which resistance occurs and will help guide treatment decisions as infected persons are referred to treatment and care.

## When will the trials begin and how are they designed?

All three of CDC's trials are scheduled to begin in early 2005 and are randomized, double-blind, placebo-controlled trials. In each trial, all participants will receive risk-reduction counseling and other prevention services, including condoms. In addition, half of the participants will be assigned by chance to receive one 300 mg tenofovir pill daily, and the other half will be assigned by chance to take one daily placebo pill (a similar pill without active medication). Neither researchers nor participants will know a participant's group assignment. This design allows the researchers to determine in a scientifically valid way whether the risks for side effects and HIV infection are different for persons taking tenofovir versus persons taking the placebo.

### *Botswana and Thailand*

The trials in Botswana and Thailand are Phase II/III safety and efficacy trials. This means that each trial will begin by examining safety alone (Phase II). After participants have completed a predetermined amount of follow-up, data will be assessed by an independent panel of experts (the data safety and monitoring board, or DSMB). If the DSMB determines that the once-daily regimen

is safe for participants, the trials will not only continue to monitor safety but will be expanded to assess whether tenofovir reduces HIV transmission (Phase III).

**Botswana:** The Botswana trial is being conducted in collaboration with the Botswana government and will enroll 1,200 HIV-negative heterosexual men and women, aged 18–29, in the nation's two largest cities, Gabarone and Francistown. Participants will be recruited at a number of venues, including HIV voluntary counseling and testing centers, sexually transmitted disease and family planning clinics, youth organizations, and community events.

**Thailand:** The Thailand trial is being conducted in collaboration with the Bangkok Metropolitan Administration and the Thailand Ministry of Public Health and will enroll 1,600 HIV-negative injection drug users (IDUs) at 17 drug-treatment clinics in Bangkok. Participants will be recruited at the drug treatment clinics and through a peer referral program.

### *United States*

The U.S. trial is a Phase II trial designed to assess the clinical and behavioral safety of once-daily tenofovir among HIV-negative men who have sex with men (MSM). The trial is being conducted at two sites in collaboration with the San Francisco Department of Public Health and the AIDS Research Consortium of Atlanta. A variety of previously successful recruitment techniques, including outreach and referrals through clinician and community-based service organizations, will be used to enroll 400 HIV-negative MSM who report having had anal intercourse during the past 12 months. To reflect the demographics of the HIV epidemic, a substantial proportion of participants will be MSM of color.

Participants will be randomly assigned to one of four study groups. Two groups will receive either tenofovir or placebo immediately; the other two groups will receive either tenofovir or placebo 9 months after enrollment. This design

will allow researchers to compare risk behaviors among persons who are and persons who are not taking a daily pill. This analysis will be critical to understanding the potential impact of a daily drug regimen on HIV risk behavior.

## **Why have these populations been selected to take part in the trials?**

It is critical to evaluate new prevention methods among the populations who most urgently need them. These and other studies of tenofovir will determine if the drug is safe and effective in reducing transmission among individuals at highest risk for HIV infection around the world.

Botswana has one of the most widespread HIV epidemics in the world: an estimated 31% of the population 15–49 years of age are infected. Data suggest that new infections are increasing most rapidly among young heterosexual men and women. It is estimated that 24% of women aged 18–19 are infected with HIV and that almost 40% of those aged 20–24 are infected. Among men, the peak seems to occur later: 11% of men aged 20–24 and 28% of men aged 25–29 are believed to be HIV infected. These data suggest very high incidence among young men and women.

In Thailand, HIV prevalence is high among injection drug users (IDUs): an estimated 42% of IDUs are already infected. A recent study found that even when HIV risk-reduction counseling was available, HIV incidence among Thai IDUs was 3% per year. Given the estimated number of IDUs in Bangkok, this incidence rate means that approximately 1,000 men and women in this city become infected through this transmission route every year.

In the United States, MSM continue to be at the greatest risk for HIV infection. Recent data from the 32 states with long-standing HIV reporting systems indicate that during 2000–2003, MSM accounted for 44% of new HIV diagnoses. During this period, new HIV diagnoses for MSM increased 11%, raising concerns that the number

of new infections may also be increasing in this population.

## **Who will be eligible to participate in the tenofovir trials?**

Because the trials are designed to determine the drug's safety and efficacy as an HIV prevention strategy, all participants will be healthy and HIV-negative. To protect the health of participants and ensure that trial data are accurate, several conditions would render some persons ineligible for participation. These include the ongoing use of prescription medication, pregnancy or breastfeeding, a history of kidney or bone disease, and participation in any other HIV clinical trial. Additional conditions, including active, untreated syphilis, hypertension, and alcohol or substance use, may also prevent some MSM from participating in the U.S. trial.

## **Are similar trials being conducted elsewhere?**

Yes. Family Health International, with funding from the Bill and Melinda Gates Foundation, is conducting similar trials of Tenofovir for HIV prevention among young women in Ghana. The National Institutes of Health will be conducting a similar trial among MSM in Peru.

## **What is the cost of the CDC studies of tenofovir?**

CDC funding of all three tenofovir HIV prophylaxis trials will total \$19 million over 3 years.

For the Botswana trial, CDC will provide a total of \$8 million in support. In Thailand, CDC's contribution will be \$7 million, and in the United States, CDC will provide \$4 million to the two institutions conducting the trial.

## **Safeguards and Services for Trial Participants**

### **What safeguards are in place to ensure protection of the volunteers?**

To ensure that each of these trials remains on a solid scientific and ethical foundation, all procedures and plans are reviewed and approved by scientific and ethical review committees at CDC (called institutional review boards, or IRBs), as well as by IRBs established by each host country and research site. Additionally, data on safety, enrollment, and efficacy will be reviewed at standard intervals by an independent data safety and monitoring board (DSMB) for the Botswana and Thai trials and by an independent safety review committee for the U.S. trial. These committees review emerging data to ensure that continuing the trial is safe and during the Phase III components, to determine the point at which the results are conclusive. If scientific questions arise during the trials, these committees will meet more frequently.

### **Will trial participants increase their risk behavior when they begin taking daily pills?**

Several critical steps are being taken to guard against this possibility. First, it is important to ensure that participants understand that trial participation may not protect them from HIV infection—because they may receive a placebo, or they may receive tenofovir, the efficacy of which remains unproven. This and other key aspects of the trial, including potential risks and benefits of participation, are explained to potential volunteers in depth in language they understand, prior to their enrollment. To ensure participants fully understand all aspects of their participation, all volunteers will be required to pass a comprehension test prior to providing written informed consent.

Second, to assist participants in eliminating or reducing HIV risk behaviors, extensive counseling will be provided at each study visit, and more

often if needed. The interactive counseling to be provided has been proven to reduce the risk of HIV and other STDs in multiple populations, including past participants of similar trials. Participants will also be offered free condoms and STD testing and treatment to reduce their risk for HIV infection. Additionally, injection drug users will be referred to, and/or offered follow-up in, a methadone treatment program and will receive bleach and instructions on how to use it to clean needles. Consistent with Thai government policy, sterile syringes will not be provided but are widely available in Thailand without a prescription and at low cost (one sterile syringe and one needle cost about 5 Thai baht, or about \$0.12).

### **How will CDC evaluate the impact of tenofovir if participants reduce their risk behavior?**

Although participants will likely be at lower risk for infection because of the prevention services received during the trial, the design of the trial will enable CDC to distinguish between the impact of these services and the impact of tenofovir. Because all participants will receive equivalent prevention services but only half will be given tenofovir, any difference in the rate of HIV infection between the two groups should be due to tenofovir.

### **What will happen to participants who do become infected during the trial?**

Despite optimal prevention counseling, some participants will become HIV infected during the trial. To ensure that infected participants are quickly referred to the best available medical and psychosocial services, they will receive free rapid HIV testing at every visit. Participants who become infected will receive confirmatory testing for infection, posttest risk-reduction and support counseling, as well as help enrolling in local HIV care programs. Both Thailand and Botswana have antiretroviral treatment and HIV care programs in place at minimal or no cost to patients. In the United States, participants will be referred to

local health care providers or public programs for needed medical and social services.

To help guide treatment decisions and to determine whether prior exposure to tenofovir affects the course of disease, testing will be provided for viral load, CD4 count, and HIV resistance mutations, and infected participants will be followed up for an additional 12 months.

## **What will happen to women who become pregnant during the trials?**

Women who express a desire to become pregnant during the trial will not be enrolled in the Thailand and Botswana trials. Participants will be counseled against becoming pregnant during the trial and will be provided free condoms. Additionally, women will take a pregnancy test at every clinic visit (at least monthly), and women who become pregnant during the trial will immediately stop taking their assigned pill. They will return for follow-up visits so that their health can be monitored.

## **What are the most common side effects associated with tenofovir?**

These trials will be among the first to evaluate the safety of tenofovir in HIV-negative persons. However, among HIV-positive persons who have taken tenofovir in combination with other antiretroviral drugs, the most common side effects are nausea, vomiting, and loss of appetite. There have also been reports of uncommon, but more serious effects, such as impaired kidney function or reductions in bone density. These effects have largely been reversible when the person stopped taking the drug. Laboratory testing will be used to carefully monitor all participants for signs of these conditions so that the drug can be stopped immediately should problems be identified. Researchers anticipate that healthy, HIV-negative participants will experience fewer side effects than do HIV-infected populations taking multiple medications.

## **Will healthcare be provided for any health problems related to the drug?**

In all three trials, researchers will monitor participants closely for drug-related side effects. If problems requiring treatment occur, participants will be quickly linked to needed medical care. Care systems differ by country.

In Botswana, the government will provide any needed medical care through the national health care system. In the United States, participants will access needed care through private health insurance or if uninsured, will be provided facilitated referrals to public health care providers. In Thailand, care will be provided in local government clinics.

## **Community Involvement in These Studies**

### **What is being done to solicit input from the communities in which these trials will be conducted?**

CDC will continue to work closely with community partners at each research site to ensure active community participation during the planning and implementation of these trials.

**Botswana:** In Botswana, community advisory boards have been established at each site. The boards comprise representatives from local governments (elected and traditional), as well as community members and representatives from key stakeholder organizations. These groups will provide input to researchers throughout the trial. Additionally, community liaisons at each site conduct outreach to community organizations and respond to any questions or concerns. Participant advisory boards will also be set up when the trial begins.

**Thailand:** In Thailand, a community relations club, composed of injection drug users, their family members, and representatives of local community organizations, meets regularly and provides advice to trial staff on all aspects of

trial design and implementation. Additionally, a community liaison will serve as a bridge between researchers and community organizations, responding to questions or concerns throughout the trial.

**United States:** In the United States, both sites have established active community advisory boards that are consulted regularly about trial procedures and educational materials for potential participants. Members of these boards will provide advice throughout the trials. Community educators at each site work to ensure that community organizations are updated on trial progress and to respond to questions or concerns.

In addition to the regular input received by these established committees, broader outreach and consultations with advocates and community-based organizations representing populations at risk for HIV have been, and will continue to be, held, as needed, to address plans for HIV prevention research and programs.

## Anticipated Results and Impact

### When will the results of the trials be available?

As eager as we are for data about this new approach for HIV prevention, results of the trial won't be available until sufficient data have been collected and analyzed to determine whether the drug is safe and effective. We are probably 2 to 4 years away from trial results. Independent panels of experts will monitor the trials closely so that the trials can be concluded as soon as definitive answers are available.

### If tenofovir does prove to be effective at preventing HIV infection in this trial, how will the drug be made available to people who need or want it?

If the efficacy trials in Botswana and Thailand prove that the drug is effective, participants in these trials and their communities will be the first to benefit. All trial participants will receive

tenofovir immediately and will continue to receive it for 1 year while CDC works with the Botswana Drugs Regulatory Unit and/or the Thai Food and Drug Administration for approval of use by the health care systems in these countries.

CDC is also working to determine how possible trial outcomes will influence future HIV prevention research, policy, and programs in the United States and worldwide. CDC will collaborate with its partners in the Department of Health and Human Services, the State Department, the Food and Drug Administration, and the World Health Organization to determine how to most effectively apply various potential results from these trials to real-world practice.

### If tenofovir proves safe and effective in one population, will it work equally well in other populations?

CDC is conducting studies in different populations to help address this question. HIV is more readily transmitted through injection drug use than through sexual exposure. The virus is transmitted more easily during rectal intercourse than during vaginal intercourse. For these reasons, the efficacy of tenofovir in reducing HIV transmission in one population may not necessarily apply to other at-risk populations.

### If studies show that tenofovir reduces the risk of HIV transmission, will people still have to practice other risk-reduction behaviors for HIV?

Yes. Regardless of the outcome, CDC will not recommend tenofovir as a first-line defense against HIV infection. Abstinence and mutual monogamy with an HIV-negative partner will remain the only 100% effective ways to prevent infection. However, if effective, this strategy could provide an additional safety net to sexually active persons at risk, when combined with reduction in the number of sexual partners, HIV counseling and testing, consistent and correct condom use, and other prevention strategies.

It is also important to remember that tenofovir will not prevent syphilis, gonorrhea, chlamydia, herpes, hepatitis, or other sexually transmitted diseases, many of which play a role in facilitating HIV transmission or speeding HIV disease progression.

### **Will support for these trials take away funding from behavioral interventions?**

Absolutely not. As we move forward with our search for new prevention strategies, it will be critical to determine how the approaches that are proven effective can best be integrated into programs. Effective behavior-change programs have greatly reduced the rate of HIV infection in the United States, and many other nations during the past 2 decades of the HIV epidemic. Because no strategy will be 100% effective in preventing HIV infection, their future impact will ultimately be determined by how effectively strategies

are used in combination to provide the greatest protection to individuals at risk. Back to Questions

### **Are physicians in certain places already prescribing tenofovir for HIV prevention?**

According to media reports, a small number of physicians in the United States and the United Kingdom are already using tenofovir in hopes of preventing HIV infection among patients in their practices. These physicians are doing so in the absence of clinical data demonstrating tenofovir's ability as a pre-exposure HIV prevention strategy.

That is why CDC is conducting these important trials—to contribute to the work of scientifically evaluating the safety and efficacy of tenofovir in the prevention of HIV transmission among persons who are at risk.

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### **For more information . . .**

#### **CDC Division of HIV/AIDS Prevention**

<http://www.cdc.gov/hiv>

*CDC HIV/AIDS prevention resources*

#### **CDC-INFO**

1-800-232-4636

*Information about personal risk and where to get an HIV test*

#### **CDC National HIV Testing Resources**

<http://www.hivtest.org>

*Location of HIV testing sites*

#### **CDC National Prevention Information Network (NPIN)**

1-800-458-5231

<http://www.cdcpin.org>

*CDC resources, technical assistance, and publications*

#### **AIDSinfo**

1-800-448-0440

<http://www.aidsinfo.nih.gov>

*Resources on HIV/AIDS treatment and clinical trials*